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(FILE 'HOME' ENTERED AT 12:23:18 ON 20 JUN 2004)

FILE 'REGISTRY' ENTERED AT 12:23:26 ON 20 JUN 2004

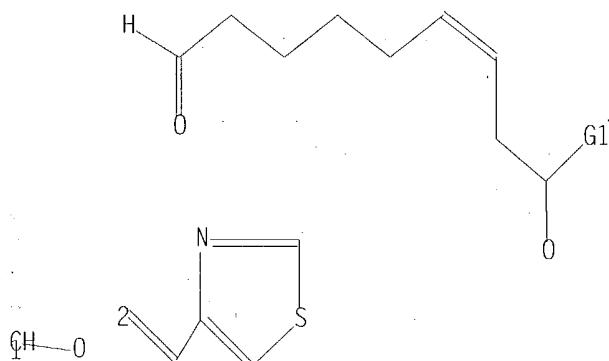
L1 STRUCTURE uploaded  
 L2 STRUCTURE uploaded  
 L3 1 S L1  
 L4 35 S L1 FULL  
 L5 1 S L2  
 L6 20 S L2 FULL

FILE 'CAPLUS' ENTERED AT 12:24:47 ON 20 JUN 2004

L7 18 S L4 AND L6

=> d que 17 stat

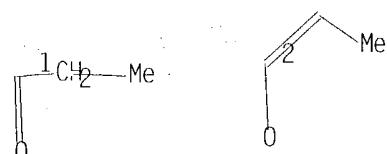
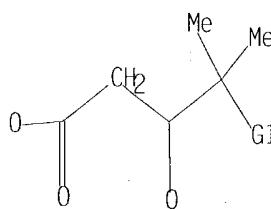
L1 STR



G1 [01].[02]

Structure attributes must be viewed using STN Express query preparation.

L2 STR



G1 [01].[02]

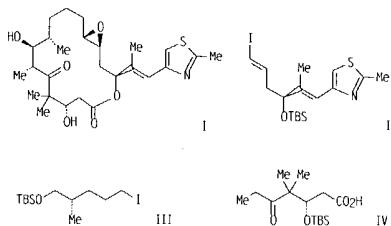
Structure attributes must be viewed using STN Express query preparation.

L4           35 SEA FILE=REGISTRY SSS FUL L1  
L6           20 SEA FILE=REGISTRY SSS FUL L2  
L7           18 SEA FILE=CAPLUS ABB=ON PLU=ON L4 AND L6

=> d 1-18 bib abs hitstr

L7 ANSWER 1 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN  
AN 2003:4456 CAPLUS

ON 138:237914  
TI The total synthesis and biological assessment of trans-epothilone A  
AU Altmann, Karl-Joern; Bold, Guido; Caravatti, Giorgio; Denzi, Donatiene; Florsheimer, Andreas; Schmidt, Alfred; Rihs, Gretel; Wartmann, Markus  
CS Corporate Research, Novartis Pharma AG, Switz.  
SO Helvetica Chimica Acta (2002), 85(11), 4086-4110  
CODEN: HCACAV; ISSN: 0018-019X  
PB Verlag Helvetica Chimica Acta  
DT Journal  
LA English  
OS CASREACT 138:237914  
GI



AB The total synthesis of (12S,13S)-trans-epothilone A (I) was achieved based on two different convergent strategies. In a first-generation approach, construction of the C(11)-C(12) bond by Pd0-catalyzed Negishi-type coupling between the C(12)-to-C(15) trans-vinyl iodide II and the C(7)-to-C(11) alkyl iodide III preceded the (nonsselective) formation of the C(5)-C(7) bond by aldol reaction between the C(7)-to-C(15) aldehyde and the dianion derived from the C(1)-to-C(6) acid IV. The lack of selectivity in the aldol step was addressed in a second-generation approach, which involved construction of the C(6)-C(7) bond in a highly diastereoselective fashion through reaction between the acetonide-protected C(1)-to-C(6) diol ("Schnizer's ketone") and the C(7)-to-C(11) aldehyde. As part of this strategy, the C(1)-C(12) bond was established subsequent to the critical aldol step and was based on B-alkyl Suzuki coupling between the C(1)-to-C(11) fragment and C(12)-to-C(15) trans-vinyl iodide II. Both approaches converged at the

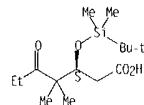
L7 ANSWER 1 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)  
stage of the 3-O, 7-O-bis-TBS-protected seco acid, which was converted to trans-deoxyepothilone A via Yamaguchi macrolactonization and subsequent deprotection. Stereoselective epoxidation of the trans C(12)-C(13) bond could be achieved by epoxidin, with Oxone in the presence of the catalyst 1,2,4,5-di-O-isopropylidene-L-erythro-2,3-hexadiuro-2,6-pyranose, which provided a 8:1 mixt. of I and its (12R,13R)-epoxide isomer (V) in 27% yield (54% based on recovered starting material). The abs. configuration of I was established by X-ray crystallog. I is at least equipotent with natural epothilone A (VI) in its ability to induce tubulin polymn. and to inhibit the growth of human cancer cell lines in vitro. In contrast, the biol. activity of V is at least two orders of magnitude lower than that of VI or I.

IT 187283-45-0P 335160-10-6P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(asym. synthesis of trans-epothilone A and its ability to induce tubulin polymerization and growth inhibition of human carcinoma)

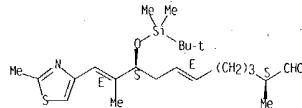
RN 187283-45-0 CAPLUS  
CN Heptanoic acid, 3-[[[(1,1-dimethylethyl)dimethylsilyloxy]-4,4-dimethyl-5-oxo- (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 335160-10-6 CAPLUS  
CN 6,10-Undecadienal, 9-[[[(1,1-dimethylethyl)dimethylsilyloxy]-2,10-dimethyl-11-(2-methyl-4-thiazolyl)-. (2S,6E,9S,10E)- (9CI) (CA INDEX NAME)

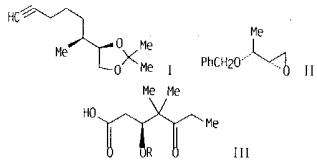
Absolute stereochemistry. Rotation (+).  
Double bond geometry as shown.



L7 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AN 2002:674000 CAPLUS  
ON 138:5571  
TI Total synthesis of epothilone A through stereospecific epoxidation of the p-methoxybenzyl ether of epothilone C  
AU Liu, Zhi-Yu; Chen, Ze-Cheng; Yu, Cheng-Zhi; Wang, Rui-Fang; Zhang, Ru-Zhou; Huang, Chu-Sheng; Yan, Zheng; Cao, De-Rong; Sun, Jian-Bo; Li, Gang  
CS Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, 200032, Peop. Rep. China  
SO Chemistry-A European Journal (2002), 8(16), 3747-3756  
CODEN: CEUEJD; ISSN: 0947-6539  
PB Wiley-VCH Verlag GmbH  
DT Journal  
LA English  
OS CASREACT 138:5571  
GI



AB The total synthesis of epothilone A is described by the coupling of four segments. Three of the segments, I, II and III (R = CH2-p-C6H4OMe), have only one chiral center; all other chiral centers were introduced by simple asym. catalytic reactions. The key steps are the ring opening of epoxide II with acetylidyne I for the construction of the C12-C13 cis double bond and a practical hydrolytic kinetic resolution (HKR) developed by Jacobsen group for the introduction the chiral center at C3. The stereospecific epoxidation of 3-O-PMB epothilone C through long-range effect of 3-O-PMB protecting group gave high yields of the C12-C13  $\alpha$ -epoxide for the synthesis of target mol.

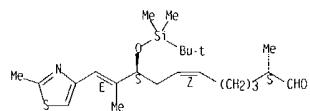
IT 188730-13-4P 327106-79-0P 331268-25-8P  
331268-26-9P 331268-27-0P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of epothilone A from the coupling of three chiral fragments including the key steps of stereoselective epoxidin, epoxide opening, and hydrolytic kinetic resolution)

RN 188730-13-4 CAPLUS  
CN 6,10-Undecadienal, 9-[[[(1,1-dimethylethyl)dimethylsilyloxy]-2,10-dimethyl-11-(2-methyl-4-thiazolyl)-. (2S,6Z,9S,10E)- (9CI) (CA INDEX NAME)

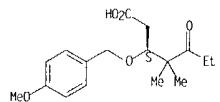
L7 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

Absolute stereochemistry. Rotation (+).  
Double bond geometry as shown.



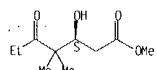
RN 327186-79-8 CAPLUS  
CN Heptanoic acid, 3-[(4-methoxyphenyl)methoxy]-4,4-dimethyl-5-oxo-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 331268-25-8 CAPLUS  
CN Heptanoic acid, 3-hydroxy-4,4-dimethyl-5-oxo-, methyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

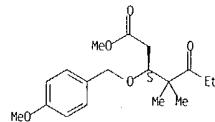


RN 331268-26-9 CAPLUS  
CN Heptanoic acid, 3-[(4-methoxyphenyl)methoxy]-4,4-dimethyl-5-oxo-, methyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

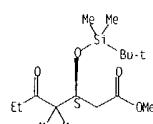
L7 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

Absolute stereochemistry. Rotation (-).  
Double bond geometry as shown.



RN 331268-27-0 CAPLUS  
CN Heptanoic acid, 3-[(1,1-dimethylethyl)dimethylsilyloxy]-4,4-dimethyl-5-oxo-, methyl ester, (3S)- (9CI) (CA INDEX NAME)

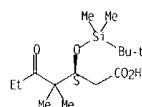
Absolute stereochemistry. Rotation (-).



IT 187283-45-0  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of epothilone A from the coupling of three chiral fragments including the key steps of stereoselective epoxidation, epoxide opening, and hydrolytic kinetic resolution)

RN 187283-45-0 CAPLUS  
CN Heptanoic acid, 3-[(1,1-dimethylethyl)dimethylsilyloxy]-4,4-dimethyl-5-oxo-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

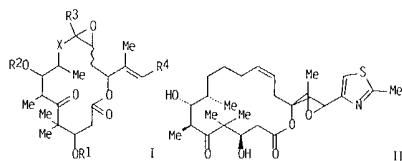
L7 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

L7 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2002-655116 CAPLUS  
DN 137:185358  
TI Preparation of epothilone analogs as anticancer agents  
IN Nicolaou, Kyriacos C.; He, Yun; Ninkovic, Sacha; Pastor, Joaquin; Roschangar, Frank; Sarabia, Francisco; Valberg, Hans; Vourloumis, Dionisios; Winslinger, Nicolas; Yang, Zhen; King, N. Paul; Finlay, M. Ray  
PA The Scripps Research Institute, USA  
SO U.S. 160 pp., Cont.-in-part of U. S. Ser. No. 856,533, abandoned.  
CODEN: USXXAM  
OT Patent  
LA English  
FAN.CNT 5

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 6441186	B1	20020827	US 1997-923869	19970904
WO 9825929	A1	19980618	WO 1997-EP7011	19971212
W I AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW, GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9857577	A1	19980703	AU 1998-57577	19971212
AU 746597	B2	20020502		
EP 944634	A1	19990929	EP 1997-953808	19971212
R I AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9714140	A	20000229	BR 1997-14140	19971212
CN 1246662	A	20000308	CN 1997-181771	19971212
CN 1134443	B	20040114		
JP 2001504856	T2	20010410	JP 1998-526247	19971212
US 6380394	B1	20020430	US 1998-102602	19980622
PTAI US 1996-32864P	P	19961213		
US 1997-855633	B2	19970514		
US 1997-923869	A2	19970904		
WO 1997-EP7011	W	19971212		
OS MARPAT 137:185358				
GI				

L7 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



AB Epothilone A, epothilone B, analogs of epothilone and libraries of epothilone analogs of formula I [R1: R2 = H, silyl group, Me, Ac, PhCO, tert-butoxycarbonyl; R3 = H, Me, ClO, (substituted) CO2H, etc.; R4 = heterocycl; etc.; X = (CH2)n; n = 1-5] are synthesized. Epothilone A and B are known anticancer agents that derive their anticancer activity by the prevention of mitosis through the induction and stabilization of microtubulin assembly. Several of the analogs are demonstrated to have a superior cytotoxic activities as compared to epothilone A or epothilone B as demonstrated by their enhanced ability to induce the polymerization and stabilization of microtubules. Thus, epothilones A and B are prepared via olefin metathesis and macrocyclization. II was prepared and showed 7% tubulin polymerization

IT 187293-45-0P

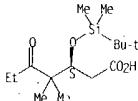
RL: CRT (Combinatorial reactant); RCT (Reactant); SPN (Synthetic preparation); CMBl (Combinatorial study); PREP (Preparation); RACT (Reactant or reagent)

(preparation of epothilone analogs as anticancer agents)

RN 187283-45-0 CAPLUS

CN Heptanoic acid, 3-[(1,1-dimethylethyl)dimethylsilyl]oxy)-4,4-dimethyl-5-oxo-, (3S)- (9CI) (CA INDEX NAME)

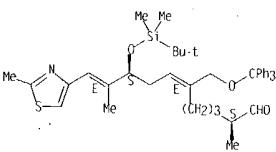
Absolute stereochemistry. Rotation (-).



IT 188730-13-4P 193146-27-9P 201136-70-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

L7 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

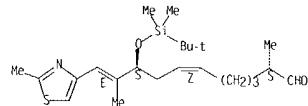
L7 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

(preparation of epothilone analogs as anticancer agents)

RN 188730-13-4 CAPLUS

CN 6,10-Undecadienal, 9-[(1,1-dimethylethyl)dimethylsilyl]oxy)-2,10-dimethyl-11-(2-methyl-4-thiazolyl)-, (2S,6Z,9S,10E)- (9CI) (CA INDEX NAME)

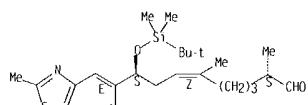
Absolute stereochemistry. Rotation (+).  
Double bond geometry as shown.



RN 193146-27-9 CAPLUS

CN 6,10-Undecadienal, 9-[(1,1-dimethylethyl)dimethylsilyl]oxy)-2,10-dimethyl-11-(2-methyl-4-thiazolyl)-, (2S,6Z,9S,10E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
Double bond geometry as shown.



RN 201136-70-1 CAPLUS

CN 6,10-Undecadienal, 9-[(1,1-dimethylethyl)dimethylsilyl]oxy)-2,10-dimethyl-11-(2-methyl-4-thiazolyl)-6-[(triphenylmethoxy)methyl]-, (2S,6Z,9S,10E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
Double bond geometry as shown.

IT 188730-13-4P 193146-27-9P 201136-70-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

L7 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2002-314889 CAPLUS

DN 136:340534

TI Method for the production of asymmetrically substituted acyloins and derivatives and for the production of epothilones B, D and their derivatives

IN Wessjohann, Ludger A.; Scheid, Günther; Bornscheuer, Uwe; Henke, Erik; Kuit, Wouter; Orru, Romano

PA Morphochem A.-G., Germany

SO PCT Int. Appl. 182 pp.

CODEN: PIXXD2

DT Patent

LA German

FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI WO 2002032844 A2 20020425 WO 2001-EP11992 20011016

WO 2002032844 C1 20030821

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10051136 A1 20020418 DE 2000-10051136 20000116

DE 10134172 A1 20030123 DE 2001-10134172 20010713

AU 2002021693 A5 20020429 AU 2002-21693 20010116

EP 1358144 A1 20031105 EP 2001-987736 20010116

R: AT, BE, CH, DE, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004082651 A1 20040429 US 2003-414510 20030415

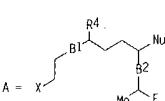
PRA1 DE 2000-10051136 A 20001016

DE 2001-10134172, A 20010713

WO 2001-EP11992 W 20011016

OS CASREACT 136:340534; MARPAT 136:340534

G1



AB The invention relates to racemic and especially non-racemic acyloins,  $R(C(=O)CHR20H)$  [I: R1 = H, alkyl (especially Me, Et, Pr), aryl, alkylaryl,

L7 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)  
 CH<sub>2</sub>-aryl. (CH<sub>2</sub>)<sub>2</sub>-aryl. vinyl. alkylnyl. propynyl. allyl. 3,3-dialkylallyl. C3-7-cycloalkyl. CH<sub>2</sub>f3-n. C3-7-oxacycloalkyl; R2 = alkyl. aryl. alkylaryl. CH<sub>2</sub>-aryl. (CH<sub>2</sub>)<sub>2</sub>-aryl. vinyl. alkylnyl. propynyl. allyl. 3,3-dialkylallyl. E- or Z-haloalkenyl. 3,3-dihaloallyl. C3-7-cycloalkyl. CH<sub>2</sub>f3-n. C3-7-oxacycloalkyl. alkylpropynyl. 1-alkylallyl. 3,3-dialkylallyl. A (joined at X); B1, B2 = single or E, Z, E/Z-double bond; B1 = epoxide; R4 = H, F, Cl, Br, I, alkyl (esp. Me, Et, CH<sub>2</sub>f3-n), aryl, alkylaryl. CH<sub>2</sub>-aryl. (CH<sub>2</sub>)<sub>2</sub>-aryl. vinyl. alkylnyl. propynyl. allyl. 3,3-dialkylallyl. C3-7-cycloalkyl. CH<sub>2</sub>f3-n. C3-7-oxacycloalkyl. E = Me, CH<sub>2</sub>OH, CH<sub>2</sub>O-PG, CHO, CO2R, CO2-PG, CH<sub>2</sub>-halo, CONR2, CON(PG)2, CON(OMe)2, CON(R), CN; R = alkyl; Nu = R4, O-PG, OR, N(PG)2, N(alkyl)2, S-PG, S-alkyl, Se-PG, Se-alkyl, CN, N3, acyl, heteroaryl; PG = protective group; their derivs., a method for the prodn. thereof and the use of the same for producing epothilones and their derivs. The invention esp. relates to the prodn. of acylins in a non-racemic form by means of diastereomer. sepn. or synthesis using auxiliary agents and by means of enzymic resoln. of racemates. The invention also relates to epothilone synthesis components, a method for the prodn. thereof and the use of synthesis components for producing epothilones and their derivs. Thus, optically active (Z)-3-hydroxy-6,10-dimethyl-11-[(tert-butylidimethylsilyl)oxy]undeca-5,9-dien-2-one was prep'd. from (+)- (Z)-3-acetoxy-6,10-dimethyl-11-[(tert-butylidimethylsilyl)oxy]undeca-5,9-dien-2-one via enzymic resoln. with Chirazyme L6. The optically active hydroxy ketone was converted to three 3-O-[(tert-butylidimethylsilyl)lepto]thione D stereoisomers.

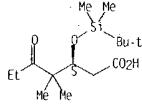
IT 187283-45-0P 415899-99-9P 415900-05-8P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of asym. substituted acylins and derivs. for the of epothilone B, D and their derivs.)

RN 187283-45-0 CAPLUS

CN Hepanoic acid, 3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4-dimethyl-5-oxo-. (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 415899-99-9 CAPLUS

CN Hepanoic acid, 6-bromo-3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4-dimethyl-5-oxo-. 4,8-dimethyl-1-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-9-oxo-3-nonenyl ester. (3S)- (9CI) (CA INDEX NAME)

L7 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2002-293380 CAPLUS

CN 136-325359

TI Methods of preparing epothilones and related analogs

IN Avery, Mitchell A.

PA The University of Mississippi, USA

SO PCT Int. Appl., 129 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN,CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002030356	A2	20020418	WO 2001-US32225	20011015
WO 2002030356	A3	20040219		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW, GH, GM, KE, LS, MH, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG				
AU 2002013248	A5	20020422	AU 2002-13248	20011015
US 2002091269	A1	20020711	US 2001-981312	20011015
EP 1414384	A2	20040506	EP 2001-981618	20011015
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
PRAI US 2000-240488P	P	20001013		
WO 2001-US32225	W	20011015		
OS MARPAT 136-325359				
GI				

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB The present invention relates to methods for preparing epothilone analogs, such as I and II [R1 = H, alkyl, alkenyl, alkylnyl, (substituted) aryl, cycloalkyl, heterocycle; R5 = H, PMB, DPS, TBS; R7 = H, TBS, TROC, CO<sub>2</sub>CH<sub>2</sub>Me; R8 = H, TBS], via an aldol condensation of III or IV [R6 = H, TBS, TMSPM, SEM], with V, VI or VII (M = alkali metal) to form condensation product followed by macrolactonization. Thus, epothilone B II (R1-R4 = Me; R7-R8 = H) was prepared via a multistep synthesis starting from (R,R)- $\alpha$ -methyl-oxiranemethanol, 1-bromo-4-methyl-4-pentene, propene and di-Et-[(2-methylthiazol-4-yl)methane]phosphonate. The present invention also provides chemical compds., and methods for producing such chemical compds., that are useful in producing I and II.

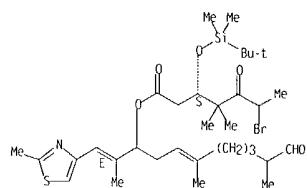
IT 193146-27-9P 380605-84-5P 412926-48-8P

412926-49-9P 412926-77-3P 412926-80-8P

L7 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

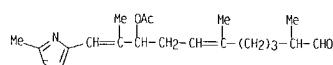
Absolute stereochemistry.

Double bond geometry as described by E or Z.



RN 415900-05-9 CAPLUS

CN 6,10-Undecadienol, 9-(acetoxy)-2,6,10-trimethyl-11-(2-methyl-4-thiazolyl)- (9CI) (CA INDEX NAME)



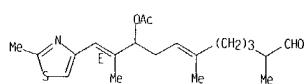
IT 415900-24-2P

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of asym. substituted acylins and derivs. for the of epothilone B, D and their derivs.)

RN 415900-24-2 CAPLUS

CN 6,10-Undecadienol, 9-(acetoxy)-2,6,10-trimethyl-11-(2-methyl-4-thiazolyl)- (10E)- (9CI) (CA INDEX NAME)

Double bond geometry as described by E or Z.



L7 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

412927-00-5P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

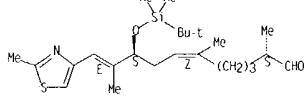
(methods for prepp. epothilone analogs and intermediates thereof)

RN 193146-27-9 CAPLUS

CN 6,10-Undecadienol, 9-[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,6,10-trimethyl-11-(2-methyl-4-thiazolyl)- (2S,6Z,9S,10E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

Double bond geometry as shown.

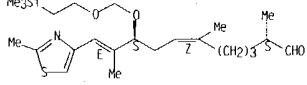


RN 380605-84-5 CAPLUS

CN 6,10-Undecadienol, 9,2,6,10-trimethyl-11-(2-methyl-4-thiazolyl)-9-[(2-trimethylsilyl)ethoxy]methoxy- (2S,6Z,9S,10E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

Double bond geometry as shown.

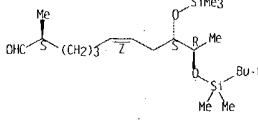


RN 412926-48-8 CAPLUS

CN 6-Undecenol, 10-[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methyl-9-[(trimethylsilyl)oxy]- (2S,6Z,9S,10R)- (9CI) (CA INDEX NAME)

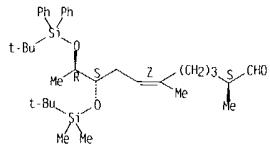
Absolute stereochemistry.

Double bond geometry as shown.



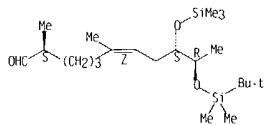
L7 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)  
 RN 412926-49-9 CAPLUS  
 CN 6-Undecenal. 9-[(1.1-dimethylethyl)dimethylsilyloxy]-10-[(1.1-dimethylethyl)diphenylsilyloxy]-2,6-dimethyl- (25.62.95.10R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.  
 Double bond geometry as shown.



RN 412926-77-3 CAPLUS  
 CN 6-Undecenal. 10-[(1.1-dimethylethyl)dimethylsilyloxy]-2,6-dimethyl-9-[(trimethylsilyloxy)-. (25.62.95.10R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.  
 Double bond geometry as shown.

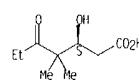


RN 412926-80-8 CAPLUS  
 CN 6-Undecenal. 10-[(1.1-dimethylethyl)dimethylsilyloxy]-9-[(4-methoxyphenyl)methoxy]-2,6-dimethyl- (25.62.95.10R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.  
 Double bond geometry as shown.

IT 188177-18-6 198571-07-8  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (methods for preparing epothilone analogs and intermediates thereof)  
 RN 188177-18-6 CAPLUS  
 CN Heptanoic acid. 3-hydroxy-4,4-dimethyl-5-oxo-. (3S)- (9CI) (CA INDEX NAME)

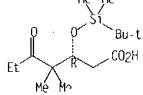
Absolute stereochemistry.



RN 198571-87-8 CAPLUS  
 CN Heptanoic acid. 3-[(1.1-dimethylethyl)dimethylsilyloxy]-4,4-dimethyl-5-oxo-. (3R)- (9CI) (CA INDEX NAME)

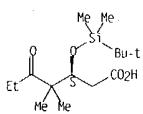
L7 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

Absolute stereochemistry.



IT 187283-45-0P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (methods for preparing epothilone analogs and intermediates thereof)  
 RN 187283-45-0 CAPLUS  
 CN Heptanoic acid. 3-[(1.1-dimethylethyl)dimethylsilyloxy]-4,4-dimethyl-5-oxo-. (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L7 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2002-291687 CAPLUS  
 DN 136:325358

TI Procedure for the production of epothilone building blocks and synthesis of epothilone B, D and derivatives

IN Wessjohann, Ludger A.; Scheid, Guenther

PA Germany

SO Ger. Offen., 20 pp.

CODEN: GAXXBX

DT Patent

LA German

FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10051136	A1	20020418	DE 2000-10051136	20001016
WO 2002032844	A2	20020425	WO 2001-EP11992	20011016
WO 2002032844	C1	20030821		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TZ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TZ, TM, RW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GH, GO, GW, ML, MR, NE, SN, TD, TG				
AU 2002021693	A5	20020429	AU 2002-21693	20011016
EP 1358144	A1	20031105	EP 2001-987736	20011016
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004082651	A1	20040429	US 2003-414510	20030415
PRA1 DE 2000-10051136, A		20001016		
DE 2001-10134172, A		20010713		
WO 2001-EP11992, W		20011016		
OS CASREACT 136:325358: MARPAT 136:325358				
GI				

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

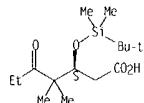
AB The invention concerns 2 types of suitable building blocks for the synthesis of epothilones and their derivs., as well as precursors of these building blocks, such as  $R'COCH(CO2R)OC(O)CH2$  (X = H, OH, Cl, Br, I,  $OSiC6H4Me-4$ ,  $035Me$ ,  $035CF3$ , alkanate, arylcarboxylate; R = H, alkyl, aryl, alkylaryl, vinyl,  $CH2F3-n$ ,  $C3-7$ -cycloalkyl,  $C3-7$ -oxacycloalkyl, H, Me, Et, Ph,  $CH2Ph$ , R" = R, especially Me). The invention further concerns the synthesis of these synthetic building blocks, whereby the synthetic building blocks are compds. with the general formula I [B1, B2, B3 = single or double bond (E, Z, E/Z mixture), epoxide, cyclopropane ring; E = Me, (un)protected  $CH2OH$ ,  $CHO$ ,  $CO2R$ ,  $CH2X$ ,  $CONR2$ ,  $CONMe2$ , CN; EWG = E, CN,  $C(O)R$ , dialkyl

L7 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)  
 phosphonate, SO2R, SO2OR, CF3, CC13, NO2; R' = R, esp. H; Y = S, NH, NR, N-protecting group, O: Z = OH, O-PG, OR, O-, N-Nu, CH-heteroaryl, -CH-aryl, -PR3; Nu = R, O-PG, OR, N(PG)2, NR2, S-PG, SR, Ser, CN, N3, aryl, heteroaryl; dashed line = single or double bond; PG = protecting group] and Y'CH(B32')C(=O)COCHX [X' = OH, Cl, Br, I, O3SC6H4Me-4, O3SMe, O3SCF3, alkanoate, arylcarboxylate; Y' = H, OH, OR, O-PG, NH2, NR2, SR, SH, N(PG)2; Z' = O, OH, OR, O-PG, NH2, NR2, N(PG)2, SR, SH, Cl, Br, C(=O)2-DG] and III. of the epothilone and of its derived compounds. The invention concerns these precursors as synthetic building blocks for epothilone analogs and in particular the synthesis of epothilones B and D and their derivs. from these precursors.

IT 187283-45-0P 412910-63-5P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation of epothilone building blocks and synthesis of epothilone B, D and analogs and derivs.)

RN 187283-45-0 CAPLUS  
 CN Heptanoic acid, 3-[[((1,1-dimethylethyl)dimethylsilyl)oxy]-4,4-dimethyl-5-oxo-, (3S)- (9CI) (CA INDEX NAME)

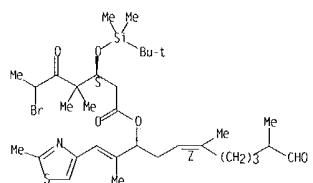
Absolute stereochemistry. Rotation (-).



RN 412910-63-5 CAPLUS  
 CN Heptanoic acid, 6-bromo-3-[[((1,1-dimethylethyl)dimethylsilyl)oxy]-4,4-dimethyl-5-oxo-, (3Z)-4,8-dimethyl-1-[(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-9-oxo-3-nonyl ester, (3S)- (9CI) (CA INDEX NAME)

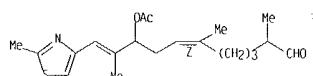
Absolute stereochemistry.  
 Double bond geometry as described by E or Z.

L7 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



IT 412043-08-4P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of epothilone building blocks and synthesis of epothilone B, D and analogs and derivs.)  
 RN 412043-08-4 CAPLUS  
 CN 6,10-Undecadienal, 9-(acetoxy)-2,6,10-trimethyl-11-(2-methyl-4-thiazolyl)-, (6Z)- (9CI) (CA INDEX NAME)

Double bond geometry as described by E or Z.



L7 ANSWER 7 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2002-132141 CAPLUS

CN 136-318924

TI Synthetic and semisynthetic analogs of epothilones: chemistry and biological activity

AU Altmann, Karl-Heinz; Blommers, Marcel J. J.; Caravatti, Giorgio; Florsheimer, Andreas; Nicolaou, Kyriacos C.; O'Reilly, Terrence; Schmidt, Alfred; Schinzer, Dieter; Wartmann, Markus  
 CS TA Oncology Research, Novartis Pharma AG, Basel, CH-4002, Switz.  
 SO ACS Symposium Series (2001), 796(Anticancer Agents), 112-130  
 CODEN: ACSM08; ISSN: 0097-6156

PB American Chemical Society

DT Journal

LA English

AB Epothilones A and B are naturally occurring microtubule depolymerizers, which exhibit potent *in vitro* antiproliferative activity. Epothilone B is a 3-30-fold more potent inhibitor of human cancer cell growth than paclitaxel in paclitaxel-sensitive cancer cell lines and in paclitaxel-resistant lines exceeds paclitaxel activity by 102-103-fold. In addition, epothilone B exhibits potent *in vivo* antitumor activity even in multidrug-resistant tumor models. In order to gain a better understanding of the structural requirements for epothilone-mediated cytotoxicity and antitumor activity and to discover analogs with similar potency but perhaps better tolerability *in vivo*, we have investigated a series of structural modifications involving the epoxide site (C12/C13) and the heterocyclic side-chain of epothilones. In this paper we present the synthesis of these analogs and we discuss the impact of such modifications on tubulin polymerization activity as well as cytotoxicity *in vitro*.

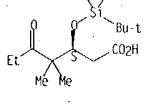
IT 187283-45-0P 335160-10-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (synthetic and semisynthetic analogs of epothilones and their chemical and biol. activity)

RN 187283-45-0 CAPLUS

CN Heptanoic acid, 3-[[((1,1-dimethylethyl)dimethylsilyl)oxy]-4,4-dimethyl-5-oxo-, (3S)- (9CI) (CA INDEX NAME)

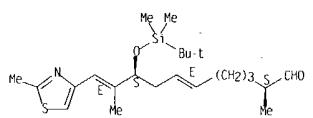
Absolute stereochemistry. Rotation (-).



RN 335160-10-6 CAPLUS  
 CN 6,10-Undecadienal, 9-[[((1,1-dimethylethyl)dimethylsilyl)oxy]-2,10-dimethyl-11-(2-methyl-4-thiazolyl)-, (2S,6E,9S,10E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

L7 ANSWER 7 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)  
 Double bond geometry as shown.



RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:752384 CAPLUS

DN 136:37430

TI Total synthesis of epothilone B

AU Valluri, Muralikrishna; Hindupur, Rama M.; Bijoy, Panicker; Labadie, Guillermo; Jung, Jae-Chul; Avery, Mitchell A.

CS Department of Medicinal Chemistry School of Pharmacy Department of Chemistry and National Center for Natural Products Research, University of Mississippi, University, MS, 38677-1848, USA

SO Organic Letters (2001), 3(23), 3607-3609

CODEN: ORLEF7; ISSN: 1523-7060

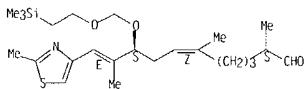
PB American Chemical Society

DT Journal

LA English

OS CASREACT 136:37430

GI

L7 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)  
(trimethylsilyl)ethoxy(methoxy)-, (2S,6Z,9S,10E)- (9CI) (CA INDEX NAME)Absolute stereochemistry, Rotation (+).  
Double bond geometry as shown.RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB A convergent and stereoselective total synthesis of epothilone B (I) is described. The key steps are Normant reaction, Wadsworth-Emmons reaction of a Me ketone II with the phosphonate reagent III, diastereoselective aldol condensation of aldehyde IV with enolate V to form the C6-C7 bond, and macrocyclization.

IT 187283-45-0 380605-84-5

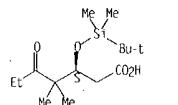
RL: RCT (Reactant); RACT (Reactant or reagent)

(stereoselective total synthesis of epothilone B via Normant, Wadsworth-Emmons, diastereoselective aldol, and macrocyclization reactions)

RN 187283-45-0 CAPLUS

CN Heptanoic acid, 3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4-dimethyl-5-oxo-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry, Rotation (-).



RN 380605-84-5 CAPLUS

CN 6,10-Undecadienal, 2,6,10-trimethyl-11-(2-methyl-4-thiazolyl)-9-[[2-

L7 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:708494 CAPLUS

DN 136:69672

TI Total synthesis of epothilone A

AU Hindupur, R. M.; Panicker, B.; Valluri, M.; Avery, M. A.

CS Department of Medicinal Chemistry, University of Mississippi, School of Pharmacy, University, MS, 38677-1848, USA

SO Tetrahedron Letters (2001), 42(42), 7341-7344

CODEN: TELEAY; ISSN: 0040-4039

PB Elsevier Science Ltd.

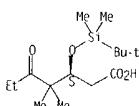
DT Journal

LA English

OS CASREACT 136:69672

GI

L7 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



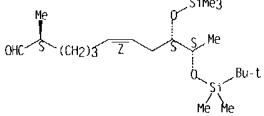
IT 383911-97-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of epothilone A via stereoselective aldol, macrocyclization, and Wadsworth-Emmons reactions)

RN 383911-97-5 CAPLUS

CN 6-Undecenal, 10-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methyl-9-[(trimethylsilyl)oxy]-, (2S,6Z,9S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A convergent total synthesis of epothilone A (I) is described. The key steps are diastereoselective aldol condensation of aldehyde II to form the C6-C7 bond; macrocyclization and Wadsworth-Emmons reaction of Me ketone with phosphonate reagent III (R = Et).

IT 187283-45-0

RL: RCT (Reactant); RACT (Reactant or reagent)

(total synthesis of epothilone A via stereoselective aldol, macrocyclization, and Wadsworth-Emmons reactions)

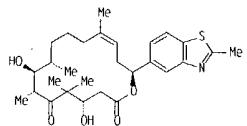
RN 187283-45-0 CAPLUS

CN Heptanoic acid, 3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4-dimethyl-5-oxo-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry, Rotation (-).

L7 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN  
 AN 2001:138738 CAPLUS  
 DN 134-311010

TI Synthetic epothilone analogs with modifications in the northern hemisphere and the heterocyclic side-chain-synthesis and biological evaluation  
 AU End. Nicole; Bold. Guido; Caravatti. Giorgio; Wartmann. Markus; Altmann. Karl-Heinz  
 CS TA Oncology Research. Novartis Pharma AG. Basel. CH-4002. Switz.  
 SO Proceedings of ECSC-3. [and] Proceedings of ECSC-4. Sept. 1-30. 1999 and 2000 (2000). Meeting Date 1999-2000. 1431-1442. Editor(s): Pombo-Villar. Esteban. Publisher: Molecular Diversity Preservation International. Basel. Switz.  
 CODEN: 69AXZT  
 DT Conference: (computer optical disk)  
 LA English  
 OS CASREACT 134-311010  
 GI



AB The authors have synthesized epothilone analogs, e.g. I, with modifications in the northern hemisphere and the heterocyclic side-chain. In all three cases the key steps for construction of the macrocyclic skeleton involve Yamaguchi macrolactonization, the build-up of the requisite seco-acid through aldol reaction between the C7-C15 aldehyde and the dianion of the O-protected C1-C6 β-hydroxy acid fragment, and the assembly of the C7-C15 aldehyde through the appropriate type of Pd(0)-catalyzed coupling reaction. The IC50 for growth inhibition of the KB-31 tumor cell line for I was 0.45 nM.

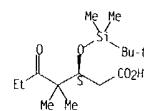
IT 187283-45-0 18817-18-6

RL: RCT (Reactant); RACT (Reactant or reagent)  
 (synthetic epothilone analogs with modifications in the northern hemisphere and the heterocyclic side-chain-synthesis and biol. evaluation)

RN 187283-45-0 CAPLUS

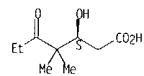
CN Heptanoic acid, 3-[(1,1-dimethyl-1-ethoxyethyl)dimethylsilyloxy]-4,4-dimethyl-5-oxo-, (3S)- (9CI) (CA INDEX NAME)

L7 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)  
 Absolute stereochemistry. Rotation (-).



RN 188177-18-6 CAPLUS  
 CN Heptanoic acid, 3-hydroxy-4,4-dimethyl-5-oxo-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

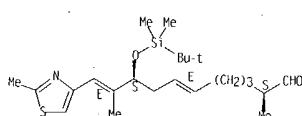


IT 335160-10-6  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation): RACT (Reactant or reagent)  
 (synthetic epothilone analogs with modifications in the northern hemisphere and the heterocyclic side-chain-synthesis and biol. evaluation)

RN 335160-10-6 CAPLUS

CN 6,10-Undecadiena, 9-[(1,1-dimethyl-1-ethoxyethyl)dimethylsilyloxy]-2,10-dimethyl-11-(2-methyl-4-thiazolyl)-, (2S,6E,9S,10E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
 Double bond geometry as shown.



RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

L7 ANSWER 11 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1999-753225 CAPLUS  
 DN 132-3284

TI Preparation of intermediates for the synthesis of epothilones  
 IN Altmann. Karl-Heinz; Bauer. Armin; Schinzer. Dieter  
 PA Novartis A.-G.. Switz.: Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.

SO PCT Int. Appl. 59 pp.  
 CODEN: PIXXD2

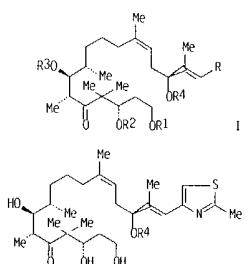
DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9959985	A1	19991125	WO 1999-EP3354	19990514
	W: AE. AL. AM. AT. AU. AZ. BA. BB. BG. BR. BY. CA. CH. CN. CU. CZ. DE. DK. EE. ES. FI. GB. GO. GE. GH. GM. HR. HU. ID. IL. IN. IS. JP. KE. KG. KP. KR. KZ. LC. LK. LR. LS. LT. LU. LV. MD. MG. MK. MW. MX. ND. NZ. PL. PT. RO. RU. SD. SE. SG. SI. SK. SL. TJ. TM. TR. TT. UA. UG. US. UZ. VN. YU. ZA. ZW. AM. AZ. BY. KG. KZ. MD. RU. TJ. TH. RW. GH. GM. KE. LS. MW. SD. SL. SZ. UG. ZW. AT. BE. CH. CY. DE. DK. ES. FI. FR. GB. GR. IE. IT. LU. MC. NL. PT. SE. BF. BJ. CF. CG. CI. CM. GA. GN. GW. ML. MR. NE. SN. TD. TG				
	AU 9942622	A1	19991206	AU 1999-42622	19990514
	EP 1080092	A1	20010307	EP 1999-952092	19990514
	R: AT. BE. CH. DE. DK. ES. FR. GB. GR. IT. LI. LU. NL. SE. PT. IE. FI				
	US 6350878	B1	20020226	US 2000-715674	20001117
PRAI	GB 1998-10659	A	1990518		
	WO 1999-EP3354	W	19990514		
	WO 1999-EP5354	A1	19990514		
OS	MARPAT 132-3284				
GI					

L7 ANSWER 11 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



AB Epothilone B intermediates, such as I (R = heterocyclic); R1, R2, R3, R4 = H, alc. protecting groups] were prepared. Thus, epothilone intermediate II (R = SiMe<sub>2</sub>CH<sub>3</sub>) was prepared in a multistep synthetic sequence from starting materials such as 5-(benzyloxy)pentanoic acid, thiocacetamide, 1,3-dichloroacetone, (5S)-*(2,2-cyclohexylidenyl)-4-oxo-1,3-dioxolan-5-*ylacetic acid, etc.

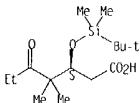
IT 187283-45-OP 193146-27-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(preparation of intermediates for the synthesis of epothilones)

RN 187283-45-0 CAPLUS

CN Heptanoic acid, 3-[[[(1,1-dimethylethyl)dimethylsilyloxy]-4,4-dimethyl-5-oxo-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 193146-27-9 CAPLUS

CN 6,10-Undecadienal, 9-[[[(1,1-dimethylethyl)dimethylsilyloxy]-2,6,10-trimethyl-11-(2-methyl-4-thiazoly)-, (2S,6Z,9S,10E)- (9CI) (CA INDEX NAME)

L7 ANSWER 12 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1999-73952 CAPLUS

DN 132:107804

TI The formal total synthesis of epothilone A

AU Kalesse, Markus; Oitschalle, Monika; Claus, Eckhard; Gerlach, Kai; Pahl, Axel; Meyer, Hartmut H.

CS Institut Organische Chemie, Univ. Hannover, Hannover, D-30167, Germany

SO European Journal of Organic Chemistry (1999), (11), 2817-2823

CODEN: EJOCFK; ISSN: 1434-193X

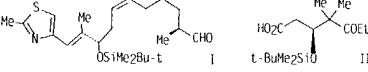
PB Wiley-VCH Verlag GmbH

DT Journal

LA English

OS CASREACT 132:107804

GI



AB The formal total synthesis of epothilone A is described. The key steps in the synthesis of the northern hemisphere are a Z-selective 10-membered ring-closing metathesis (RCM) and the diastereoselective alkylation at C(8). Aldehyde I is formed by introduction of the thiazole moiety by a Wittig reaction and subsequent functional group transformation. An efficient route to keto aldehyde II is described.

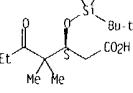
IT 187283-45-OP 188730-13-4P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(formal total synthesis of epothilone A)

RN 187283-45-0 CAPLUS

CN Heptanoic acid, 3-[[[(1,1-dimethylethyl)dimethylsilyloxy]-2,10-dimethyl-5-oxo-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



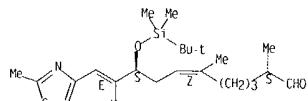
RN 188730-13-4 CAPLUS

CN 6,10-Undecadienal, 9-[[[(1,1-dimethylethyl)dimethylsilyloxy]-2,10-dimethyl-11-(2-methyl-4-thiazoly)-, (2S,6Z,9S,10E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

L7 ANSWER 11 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

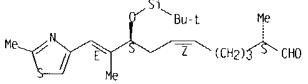
Absolute stereochemistry. Rotation (+).  
Double bond geometry as shown.



RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 12 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

Double bond geometry as shown.



RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 13 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1999-126888 CAPLUS

DN 130-196529

TI Preparation of new epothilone derivatives as pharmaceutical agents

IN Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner; Buchmann, Bernd; Schirmer, Michael

PA Schering Aktiengesellschaft, Germany

SO PCT Int. Appl., 185 pp

CODEN: PIXXD2

DT Patent

LA German

FAN.CNT 4

PATENT NO. KIND DATE APPLICATION NO. DATE

PI WO 9907692 A2 19990218 WO 1998-EP5064 19980810  
 WO 9907692 A3 19990514

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW, GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

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 DE 17748928 A1 19990429 DE 1997-19748928 19971024  
 DE 19749717 A1 19990506 DE 1997-19749717 19971031  
 DE 19751200 A1 19990520 DE 1997-19751200 19971113  
 DE 19813821 A1 19990223 DE 1998-19813821 19980320  
 AU 9893409 A1 19990301 AU 1998-93409 19980810  
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 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

JP 2001512723 T2 20010828 JP 2000-506196 19980810  
 ZA 9810403 A 20000515 ZA 1998-10403 19981113  
 US 2003144523 A1 20030731 US 2000-485292 20000503

PRAI DE 1997-19735574 A 19970809

DE 1997-19735575 A 19970809

DE 1997-19735578 A 19970809

DE 1997-19748928 A 19971024

DE 1997-19749717 A 19971031

DE 1997-19751200 A 19971113

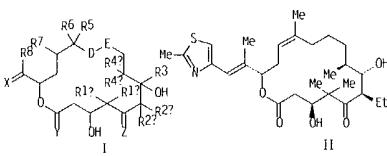
DE 1998-19813821 A 19980320

WO 1998-EP5064 W 19980810

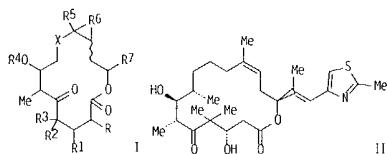
OS MARPAT 130:196529

GI

L7 ANSWER 13 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L7 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



AB Epothilone A, epothilone B, analogs of epothilone and libraries of epothilone analogs of formula I ( $X = \text{CH}_2$ ;  $n = 1-5$ ;  $R1 = \text{OH}, \text{OCH}_3$ ; absent;  $R2, R3 = \text{H}, \text{CH}_2, \text{Me}$ ;  $R4 = \text{H}, \text{Me}$ ; protecting group:  $R5 = \text{H}, \text{Me}, \text{CHO}$  (substituted)  $\text{CO}_2\text{H}$ , etc.;  $R6 = \text{O}, \text{CH}_2$ ; absent;  $R7 = \text{thiazolealkyl}$ , etc.) are synthesized. Epothilone A and B are known anticancer agents that derive their anticancer activity by the prevention of mitosis through the induction and stabilization of microtubulin assembly. Several of the analogs are demonstrated to have a superior cytotoxic activity as compared to epothilone A or epothilone B as demonstrated by their enhanced ability to induce the polymerization and stabilization of microtubules. Thus, II was prepared and was shown to induce tubulin polymerization at 94% relative to GTP, and inhibit carcinoma cell growth.

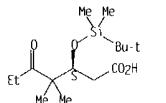
IT 187283-45-0P 188730-13-4P 193146-27-9P

201136-70-1P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(preparation of epothilone analogs as anticancer agents)

RN 187283-45-0 CAPLUS

CN Heptanoic acid, 3-[(1.1-dimethylethyl)dimethylsilyloxy]-4,4-dimethyl-5-oxo-, (3S)- (9CI) (CA INDEX NAME)

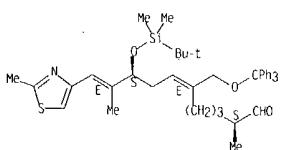
Absolute stereochemistry. Rotation (-).



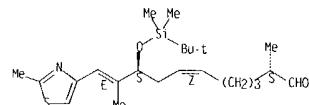
RN 188730-13-4 CAPLUS

CN 6,10-Undecadienal, 9-[(1.1-dimethylethyl)dimethylsilyloxy]-2,10-dimethyl-11-(2-methyl-4-thiazoyl)-, (25.6Z,95.10E)- (9CI) (CA INDEX NAME)

L7 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

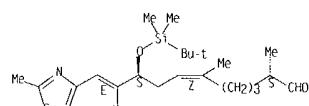
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

Absolute stereochemistry. Rotation (+).  
Double bond geometry as shown.

RN 193146-27-9 CAPLUS

CN 6,10-Undecadienal, 9-[(1.1-dimethylethyl)dimethylsilyloxy]-2,6,10-trimethyl-11-(2-methyl-4-thiazoyl)-, (2S,6Z,95.10E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
Double bond geometry as shown.

RN 201136-70-1 CAPLUS

CN 6,10-Undecadienal, 9-[(1.1-dimethylethyl)dimethylsilyloxy]-2,10-dimethyl-11-(2-methyl-4-thiazoyl)-6-[(triphenylmethoxy)methyl]-, (25.6E,95.10E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
Double bond geometry as shown.

L7 ANSWER 15 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1997-724919 CAPLUS

DN 127-346221

TI Synthesis of epothilones A and B in solid and solution phase. [Erratum to document cited in CA127:4950]

AU Nicolaou, K. C.; Winsinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E.

CS Dep. Chemistry, Skaggs Inst. Chem. Biology, Scripps Res. Inst., La Jolla, CA, 92037, USA

SO Nature (London) (1997), 390(6655), 100

CODEN: NATUAS ISSN: 0028-0836

PB Macmillan Magazines

DT Journal

LA English

AB Reference 19, includes, in addition to a total synthesis of epothilone B, biol. data for compound 23 and other congeners similar to the reported in the Letter.

IT 187283-45-0

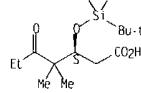
RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of a combinatorial library via solid-phase synthesis of epothilone A and solution-phase synthesis of epothilone B (Erratum))

RN 187283-45-0 CAPLUS

CN Heptanoic acid, 3-[(1.1-dimethylethyl)dimethylsilyloxy]-4,4-dimethyl-5-oxo-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT 190370-04-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

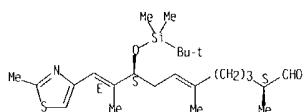
(preparation of a combinatorial library via solid-phase synthesis of epothilone A and solution-phase synthesis of epothilone B (Erratum))

RN 190370-04-8 CAPLUS

CN 6,10-Undecadienal, 9-[(1.1-dimethylethyl)dimethylsilyloxy]-2,6,10-trimethyl-11-(2-methyl-4-thiazoyl)-, (25.95.10E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as described by E or Z.

L7 ANSWER 15 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

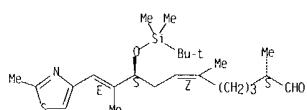


L7 ANSWER 16 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN  
 AN 1997-528753 CAPLUS  
 DN 127-135660  
 TI Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy  
 AU Nicolau, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Valberg, H.; Finlay, M. R. V.; Yang, Z.  
 CS Department of Chemistry and The Skaggs Institute for Chemical Biology, La Jolla, CA, 92037, USA  
 SO Journal of the American Chemical Society (1997), 119(34), 7974-7991  
 CODEN: JACSAT; ISSN: 0002-7863  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CASREACT 127:135660  
 GI

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

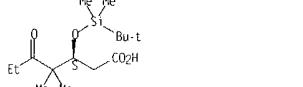
AB The total syntheses of epothilones A (I) ( $R = H$ ) and B (I) ( $R = Me$ ) and several analogs are described. The reported strategy relies on a macrolactonization approach and features selective epoxidation of the macrocycle double bond in precursors II ( $R = H, Me$ ) as well as high convergency and flexibility. Building blocks (S)-MeCH<sub>2</sub>CO(Me)CH<sub>2</sub>CH(OSiMe<sub>2</sub>Me<sub>3</sub>)CH<sub>2</sub>CO<sub>2</sub>H, (S)-Me<sub>3</sub>Me<sub>2</sub>SiOCH<sub>2</sub>CH(Me)CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>R ( $R = H, Me$ ), (III) [ $R_2 = CH_2CH_2P(OPh)_3$ ;  $CH_2CHO$ ] were constructed by asym. processes and coupled via Wittig, aldol, and macrolactonization reactions to afford the basic skeleton of epothilones and that of several of their analogs by a relatively short route. The utilization of intermediate III [ $R_2 = (E)-CH_2CH=C(Me)CH_2CH_2CH_2I$ ], obtained via a stereoselective Wittig reaction and its Enders coupling to SAMP hydrazone, in combination with a stereoselective aldol reaction with the modified substrate (S)-MeCH<sub>2</sub>CO(Me)CH<sub>2</sub>CH(OSiMe<sub>2</sub>Me<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>OSiMe<sub>2</sub>Me<sub>3</sub> improved the stereoselectivity and efficiency of the total synthesis of these new and highly potent microtubule binding antitumor agents.  
 IT 187283-45-0P 188730-13-4P 190370-04-8P  
 193146-27-9P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (total syntheses of epothilones A and B via a macrolactonization-based strategy)  
 RN 187283-45-0 CAPLUS  
 CN Heptanoic acid, 3-[(1,1-dimethylethyl)dimethylsilyloxy]-4,4-dimethyl-5-oxo-, (3S)- (9CI) (CA INDEX NAME)

L7 ANSWER 16 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



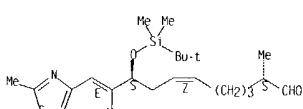
L7 ANSWER 16 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

Absolute stereochemistry. Rotation (-).



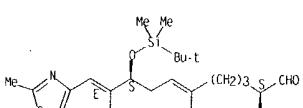
RN 188730-13-4 CAPLUS  
 CN 6,10-Undecadienol, 9-[(1,1-dimethylethyl)dimethylsilyloxy]-2,10-dimethyl-11-(2-methyl-4-thiazolyl)-, (2S,6S,10E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
 Double bond geometry as shown.



RN 190370-04-8 CAPLUS  
 CN 6,10-Undecadienol, 9-[(1,1-dimethylethyl)dimethylsilyloxy]-2,6,10-trimethyl-11-(2-methyl-4-thiazolyl)-, (2S,9S,10E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.  
 Double bond geometry as described by E or Z.



RN 193146-27-9 CAPLUS  
 CN 6,10-Undecadienol, 9-[(1,1-dimethylethyl)dimethylsilyloxy]-2,6,10-trimethyl-11-(2-methyl-4-thiazolyl)-, (2S,6S,10E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
 Double bond geometry as shown.

L7 ANSWER 17 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1997-330310 CAPLUS

DN 127:4950

TI Synthesis of epothilones A and B in solid and solution phase

AU Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E.

CS Dep. Chemistry, Skaggs Inst. Chem. Biology, Scripps Res. Inst., La Jolla, CA, 92037, USA

SO Nature (London) (1997), 387(6630), 268-272

CODEN: NATLAS; ISSN: 0028-0836

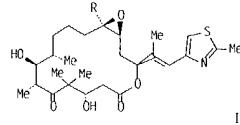
PB Macmillan Magazines

DT Journal

LA English

OS CASREACT 127:4950

GI



I

AB Epothilones A (I; R = H) and B (I; R = Me), two compds. that were recently isolated from myxobacterium Sorangium cellulosum strain 90, have generated intense interest among chemists, biologists and clinicians owing to the structural complexity, unusual mechanism of interaction with microtubules and anticancer potential of these mols. Like taxol, they exhibit cytotoxicity against tumor cells by inducing microtubule assembly and stabilization, even in taxol-resistant cell lines. Following the structural elucidation of these mols. by X-ray crystallog. in 1996, several syntheses of epothilones A and B have been reported, indicative of the potential importance of these mols. in the cancer field. Here we report the first solid-phase synthesis of epothilone A, the total synthesis of epothilone B, and the generation of a small epothilone library. The solid-phase synthesis applied here to epothilone A could open up new possibilities in natural-product synthesis and, together with solution-phase synthesis of other epothilones, paves the way for the generation of large combinatorial libraries of these important mols. for biol. screening.

IT 187283-45-0

RL: RCT (Reactant); RACT (Reactant or reagent)

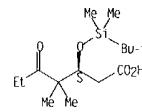
(preparation of a combinatorial library via solid-phase synthesis of

L7 ANSWER 17 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued) epothilone A and soln.-phase synthesis of epothilone B

RN 187283-45-0 CAPLUS

CN Heptanoic acid, 3-[(1,1-dimethylethyl)dimethylsilyloxy]-4,4-dimethyl-5-oxo-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT 190370-04-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation): RACT

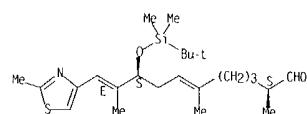
(Reactant or reagent) (preparation of a combinatorial library via solid-phase synthesis of epothilone A and solution-phase synthesis of epothilone B)

RN 190370-04-8 CAPLUS

CN 6,10-Undecadienal, 9-[(1,1-dimethylethyl)dimethylsilyloxy]-2,6,10-trimethyl-11-(2-methyl-4-thiazoly)-, (2S,9S,10E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as described by E or Z.

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 18 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1997-206419 CAPLUS

DN 126:251010

TI Total synthesis of epothilone A: the macrolactonization approach

AU Nicolaou, K. C.; Sarabia, Francisco; Ninkovic, Sacha; Yang, Zhen

CS Dep. Chem., Skaggs Inst. Chem. Biol., Scripps Res. Inst., La Jolla, CA, 92037, USA

SO Angewandte Chemie, International Edition in English (1997), 36(5), 525-527

CODEN: ACIEAY; ISSN: 0570-0833

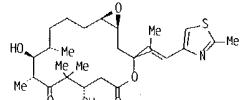
PB VCH

DT Journal

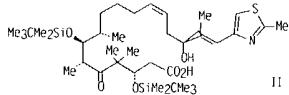
LA English

OS CASREACT 126:251010

GI



I



II

AB Epothilone A (I) was prepared via a highly convergent and flexible route with macrolactonization of hydroxy acid II as the key step.

IT 187283-45-0

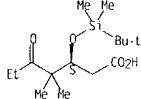
RL: RCT (Reactant); RACT (Reactant or reagent)

(total synthesis of epothilone A via a macrolactonization approach)

RN 187283-45-0 CAPLUS

CN Heptanoic acid, 3-[(1,1-dimethylethyl)dimethylsilyloxy]-4,4-dimethyl-5-oxo-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



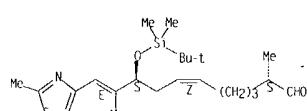
L7 ANSWER 18 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

IT 188730-13-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation): RACT  
(Reactant or reagent) (total synthesis of epothilone A via a macrolactonization approach)

RN 188730-13-4 CAPLUS

CN 6,10-Undecadienal, 9-[(1,1-dimethylethyl)dimethylsilyloxy]-2,10-dimethyl-11-(2-methyl-4-thiazoly)-, (2S,6S,9S,10E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
Double bond geometry as shown.RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT